Review Article

The Unravelling Link between Chronic Kidney Disease and Hepatitis C Infection

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The 2011 report of the World Health Organization General Assembly on noncommunicable diseases identified chronic kidney disease as a worldwide health issue posing a heavy economic burden. Hepatitis C virus infection, which is responsible for over 1 million deaths resulting from cirrhosis and liver cancer, is linked to chronic kidney disease in several ways; some forms of renal disease are precipitated by hepatitis C and patients with end-stage chronic renal disease are at increased risk for acquiring HCV. The aim of this review is to update the evidence on the relationship between hepatitis C infection and chronic kidney disease. Information has been accumulated in the last decade indicating that HCV plays an adverse effect on the incidence and progression of chronic kidney disease; a novel meta-analysis of observational studies (seven longitudinal studies; 890,560 unique individuals) found a relationship between hepatitis C seropositivity and incidence of reduced estimated glomerular filtration rate (adjusted relative risk, 1.70; 95% CI, 1.20; 2.39; $P = 0.002$) in the adult general population. In addition to conventional risk factors, hepatitis C may be an additional factor for the development of chronic kidney disease, and an atheromasic activity of hepatitis C virus has been mentioned. The link between hepatitis C and atherosclerosis could also explain the excess risk of cardiovascular mortality that has been observed among hepatitis C virus seropositive patients undergoing maintenance dialysis. A number of biologically plausible mechanisms related to hepatitis C virus have been hypothesized to contribute to atherosclerosis. Implementation of effective treatment intervention towards hepatitis C is required to decrease the healthcare burden of hepatitis C and to prevent the progression of chronic renal disease.

1. Introduction

Noncommunicable diseases (NCDs) have replaced communicable diseases as the most common causes of morbidity and premature mortality worldwide [1, 2]. By 2015, cardiovascular disease and diabetes are expected to reduce global gross domestic product by 5%; this gives emphasis on the enormous global economic impact of NCDs. Four NCDs (cardiovascular disease, cancer, diabetes, and chronic respiratory disease) have been prioritized in the Global NCD Action Plan endorsed by the World Health Assembly in 2008 because they share behavioural risk factors amenable to public health action and, together, represent a major portion of the global NCD burden [3]. Although chronic kidney disease (CKD) is absent from the World Health Organization (WHO) priority NCDs (heart disease, diabetes, chronic

respiratory disease, and cancer), compelling information exists that chronic kidney disease is a key determinant of the poor health outcomes of major noncommunicable diseases (particularly diabetes and cardiovascular disease) and the WHO has recently recommended the prevention of CKD within national NCD programs at the primary-care level [4].

The prevalence of CKD, defined by a reduction in glomerular filtration rate and increased urinary albumin excretion, exceeds 10% of the adult general population [5], and information in the last decade has shown a good association between chronic renal disease and hepatitis C virus (HCV) infection [6], which has an estimated prevalence of 3% in the world population (more than 170 million people worldwide chronically infected with HCV) [7]. The association between CKD and HCV occurs by several ways; in addition to conventional risk factors for chronic kidney disease such

TABLE 1: CKD stages according to eGFR and ACR.

CKD stages	eGFR (mL/min/1.73 m ²)	ACR (mg/g)
1	≥90	≥30
2	60–89	≥30
3	30–59	—
4	15–29	—
5	<15	—

ACR: albumin creatinine ratio; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

as aging, metabolic syndrome, arterial hypertension, and diabetes mellitus, HCV infection may be an additional risk factor.

The aim of this review is to update the evidence on the relationship between HCV infection and prevalence (or severity) of chronic kidney disease; the most recent insights on HCV infection both as a cause and complication of chronic kidney disease have been reviewed.

2. Chronic Kidney Disease: Definition and Clinical Implications

The definition of CKD has been made first in 2002 when the medical community agreed on a uniform definition (and staging) of chronic renal disease, based on measures of kidney function and independent of the cause of impaired kidney function [8]. The rising incidence and prevalence of chronic renal failure and its associated high costs and poor outcomes prompted nephrologists to issue international guidelines to define chronic kidney disease. As listed in Table 1, chronic kidney disease has been defined by reduced glomerular filtration rate (<60 mL/min/1.73 m²) for three months or more and/or proteinuria [8].

Chronic renal disease has been recognized as a worldwide health problem that affects 10–15% of the adult general population worldwide, and the overall prevalence of CKD at least equals that of diabetes. According to the 1999–2004 National Health and Nutrition Examination Survey (NHANES) III data, the prevalence of CKD was 16.8% in the US population aged ≥20 years, compared with 14.5% from the 1988–1994 NHANES, suggesting that CKD is a growing health problem in the United States [13]. NHANES is a nationally representative sample of noninstitutionalized adults living in the USA and aged 20 years or older ($n = 13,233$). As with many other chronic diseases, the prevalence of CKD increases with age, exceeding 20% in individuals older than 60 years and 35% in those older than 70 years.

The clinical and public health importance of CKD became soon apparent when large surveys showed that even early stage kidney disease is associated with adverse outcomes including increased risk of mortality and cardiovascular morbidity. Go et al. [14] in a large, community-based population ($n = 1,120,295$ adults) observed that the graded decrease of estimated glomerular filtration rate (GFR) was independently associated with the adjusted hazard ratio (aHR) for death, cardiovascular events, and hospitalization. The aHR for death

was 1.2 (95% CI, 1.1; 1.2) with an estimated GFR of 45 to 59 mL/min, 1.8 (95% CI, 1.7; 1.9) with an eGFR of 30 to 44 mL/min, 3.2 (95% CI, 3.1–3.4) with an estimated GFR of 15 to 29 mL/min, and 5.9 (95% CI, 5.4; 6.5) with an estimated GFR less than 15 mL/min. CKD is also associated with decreased quality of life, cognitive dysfunction, and increased health-care expenditures [1, 2].

3. Chronic Kidney Disease and Its Global Perspective

One potential outcome of chronic kidney disease is end-stage renal disease (ESRD) which requires renal replacement therapy (i.e., maintenance dialysis and renal transplantation). Renal replacement therapy is very costly; thus, ESRD is an important cost driver for health-care systems of developed countries and over 2 million people now need renal replacement therapy to sustain life. The majority of patients undergoing renal replacement treatment are in five countries (Brazil, Italy, Japan, Germany, and the USA) that constitute 12% of the world population. 20% undergo renal replacement therapy in about 100 developing countries that make up over 50% of the world population. These data highlight the relationship between gross domestic product and availability of renal replacement therapy; also, the high burden of ESRD and associated costs is emphasized.

Over the past 15 years, evidence from clinical trials and meta-analyses has shown that the presence of CKD dramatically increases the risk of adverse outcomes among people with other NCDs. Chronic renal disease strongly predisposes to hypertension [15] and cardiovascular disease [16]; diabetes [17], hypertension [18], and cardiovascular disease [19] are all major causes of CKD; major risk factors for diabetes [1], hypertension [1], and cardiovascular disease (such as obesity, and smoking) [20] also cause or exacerbate chronic renal disease; finally, treatments for slowing progression of CKD also reduce complications from diabetes, hypertension, and cardiovascular disease [21].

All acute and chronic diseases have a worse prognosis in the presence of kidney disease, and this is of particular relevance for cardiovascular diseases such as stroke, heart failure, and acute myocardial infarction [5]. Chronic renal disease also worsens the prognosis of patients with diabetes and pulmonary and metabolic disease. Presence of kidney disease affects patient management; for example, patients with kidney disease can experience restrictions in the use of imaging procedures requiring the application of radiocontrast agents or gadolinium and this can lead to underdiagnosis in patients with CKD [5]. Uncertainty in drug dosing including drug toxicity and underdosing is another potential source of dismal prognosis in CKD population.

Given that CKD is usually asymptomatic until later stages of the disease (stage 4 or more), a lack of awareness of earlier stages of CKD exists and risk factors for CKD are frequently underrecognized. The lack of awareness may extend to clinical physicians. Prior studies have demonstrated that early identification and management of CKD reduce the risk of progression to kidney failure and cardiovascular disease by up to 50% [22].

4. HCV-Associated Kidney Disease

In addition to conventional risk factors, other causes of chronic renal disease including drugs or alternative medications have been cited. The role of HCV in the course, morbidity, and mortality of renal disease is often not appropriately considered in the care of patients with CKD; however, HCV infection has been proposed as a possible cause of CKD. HCV has been identified in 1989 and was recognized soon as the main cause of non-A and non-B hepatitis [7]. In Western Europe, HCV prevalence ranges from 0.4 to 3%; prevalence is higher in Eastern Europe and the Middle East, up to 13% in Egypt. More than 170 million people worldwide are chronically infected with the hepatitis C virus (HCV) which is currently one of the major causes of chronic liver disease worldwide and remains a major global health burden. The long-term hepatic impact of HCV infection includes chronic hepatitis and cirrhosis, with or without hepatocellular carcinoma (HCC). Several extrahepatic manifestations have been associated with HCV infection, including haematological, dermatologic, autoimmune, and kidney diseases. HCV infection is frequently asymptomatic; thus, most chronically infected individuals have no knowledge of their infection [7].

There is increasing evidence of an association between HCV infection and glomerular disease in both native kidneys [23–25] and after kidney [26] or liver [27, 28] transplant. The most common type of HCV-related glomerulonephritis is type I membranoproliferative glomerulonephritis usually in the context of type II cryoglobulinemia [29]. HCV-infected patients show less common glomerular diseases including membranoproliferative glomerulonephritis without cryoglobulinemia, membranous nephropathy, focal segmental sclerosis, mesangial glomerulonephritis, and fibrillary and immunotactoid glomerulopathies. Anecdotal information has been reported on HCV-associated IgA nephropathy and cryoglobulinemic thrombotic microangiopathy [29]. In addition to glomerular disease, tubulointerstitial injury has been also observed in association with HCV infection [30]. Various surveys have evaluated the frequency of anti-HCV seropositive status in patients with biopsy-proven glomerulonephritis [31, 32] but the most important report on the epidemiology of HCV-associated glomerular disease has been conducted by El-Serag et al. [33]. They carried out a hospital-based case control study that enrolled all cases of HCV-infected patients hospitalized during the 1990s ($n = 34, 204$) and randomly chosen control male individuals without HCV ($n = 136, 816$) matched with cases on the year of admission. As expected, cryoglobulinemia was more common in cases than controls (0.57% versus 0.05%, $P < 0.0001$), and a greater prevalence of membranoproliferative glomerulonephritis (0.36% versus 0.05%) but not membranous nephropathy (0.33% versus 0.19%) was observed in HCV-infected individuals.

A recent meta-analysis of clinical studies (four clinical studies with 81,286 unique individuals) demonstrated that HCV seropositive status was an independent and significant risk factor for proteinuria in the general population, with a summary estimate for adjusted relative risk of 1.47 (95% CI, 1.12; 1.94; $P = 0.006$). Significant heterogeneity occurred

($R_i = 0.82$; P -value by Q test, <0.001) [34]. Proteinuria clusters with the metabolic syndrome and surveys have reported a relationship between proteinuria and individual components of the metabolic syndrome (insulin resistance, hyperglycemia, dyslipidemia, abdominal obesity, and arterial hypertension). Because patients with HCV are known to have higher prevalence of components of the metabolic syndrome, it has been hypothesized that individuals with HCV may have high frequency of proteinuria. The persistence of the relationship between HCV and proteinuria after correction for several confounding parameters including metabolic syndrome elements is in keeping with the occurrence of HCV-associated cryoglobulinemic or intrinsic renal disease.

The main clinical manifestations of HCV-associated glomerular disease are the presence of proteinuria and microscopic hematuria with or without impaired kidney function. It has been recommended by the KDIGO HCV guidelines that patients infected with HCV be tested at least annually for proteinuria, hematuria, and eGFR [29]. HCV-infected patients with clinical evidence of glomerulonephritis should undergo kidney biopsy and the outcome of HCV-associated glomerulonephritis is improved by early diagnosis and therapy. The routine laboratory diagnosis of HCV-related glomerulonephritis is based on the presence of conventional markers of HCV infection such as anti-HCV antibody and HCV viraemia (HCV RNA). The disappearance of proteinuria after interferon therapy with clearance of HCV RNA from serum strongly suggests the pathogenic role of HCV in this type of glomerular disease [29].

Studies are under way to assess whether HCV-associated glomerular disease could be related to occult HCV infection (i.e., detectable viral RNA in peripheral blood mononuclear cells or in serum after ultracentrifugation); occult HCV occurs only in anti-HCV negative patients with no detectable HCV RNA in serum. Occult HCV infection has been observed in various patient groups such as hemodialysis patients, patients with cryptogenic hepatitis and liver cirrhosis, hepatocellular carcinoma, lymphoproliferative disorders, and healthy individuals without evidence of liver disease. The role played by occult HCV infection in the development of HCV-associated glomerular disease is in keeping with some pieces of evidence; for example, interferon based therapy has given benefit in some cases of HCV negative cryoglobulinemic glomerulonephritis [35]. HCV antigens or particles have been found in the kidney tissue of patients with HCV negative glomerulonephritis [36]. If confirmed, occult HCV infection could be the underlying cause of glomerular disease in some patients with negative serologic viral markers, and detection of occult HCV might be the rationale for antiviral therapy in anti-HCV negative glomerular nephropathy.

5. Mechanisms of HCV-Associated Renal Injury

The mechanisms of HCV-related renal disease are uncertain and research has suggested various causes including a direct cytopathic activity of HCV on renal parenchyma [37]. Renal parenchyma expresses CD8 and SR-B1 receptors that

allow binding of HCV to the cell surface and endocytosis. Hepatitis C virus-related proteins have been identified in mesangial cells, tubular epithelial cells, and endothelial cells of glomerular and tubular capillaries [38]. An association between greater proteinuria and mesangial deposition of HCV RNA and related proteins has been suggested; this possibly mirrors a direct mesangial injury by HCV [39].

Much more is known about kidney injury due to systemic immune response to HCV infection that is mediated by cryoglobulins (a group of globulins with the common property of precipitating from cooled serum). Persistent HCV infection gives overstimulation of B-lymphocytes and production of mixed cryoglobulins which are mainly composed of a polyclonal immunoglobulin (Ig), either IgG or IgM, bound to another Ig that works as an antirheumatoid factor (RF) [40–42]. HCV-associated glomerular injury can result from deposition of circulating immune complexes containing HCV proteins, anti-HCV antibody, and rheumatoid factor IgM. Cryoglobulins are frequently deposited in the mesangium and their nephrotoxicity is related to affinity of the IgM-k-RF for cellular fibronectin in the mesangial matrix. Deposition of cryoglobulins in the glomerular capillaries appears as eosinophilic material which is stained with antisera to IgM, C3, and fibrin by immunofluorescence. Cryoglobulins may also induce endothelitis via anti-endothelial antibody activity and complement activation; an overexpression of VCAM-1 has been found with platelet aggregation. Viral HCV antigens have been found by immunochemistry and by *in situ* hybridization. Some authors have used laser microdissection to detect HCV RNA genomic sequences of HCV core protein in glomeruli and tubules of patients with HCV-associated glomerular disease [39].

Recently, an elevation of toll-like receptor 3 (TLR3) messenger RNA expression has been seen in glomeruli, particularly mesangial cells, of patients with HCV-induced GN, this being associated with an increased activity of some proinflammatory cytokines. A greater TLR3 expression was observed in peripheral mononuclear cells of patients with HCV positive GN ($n = 46$) than HCV negative patients ($n = 32$) or healthy individuals ($n = 20$), $P < 0.0001$ [43]. TLRs are primary proteins expressed on immune and nonimmune cells as key components of the innate immune system. TLRs recognize molecular patterns associated with microbial agents and give an immune response [44].

Nonimmunologically mediated mechanisms of kidney disease have been also hypothesized. Anti-HCV positive patients, with or without cirrhosis, show raised levels of fasting serum insulin and insulin resistance and greater prevalence of diabetes mellitus. HCV core protein directly reduces expression of insulin receptor substrate proteins (IRS) 1 and 2 which are involved in the metabolic activities of insulin and stimulate activation of IRS-1 and high expression of TNF- α at least in hepatic cells [45, 46]. Insulin resistance and hyperinsulinemia give excess intrarenal synthesis of IGF-1 and TGF β , thus promoting proliferation of renal cells and upregulating the expression of angiotensin II type 1 receptors in mesangial cells. The deleterious activities of angiotensin II at kidney level are enhanced. An excess local production of endothelin-1, reduced endothelial synthesis of nitric oxide,

and increased oxidative stress have been implicated in the pathogenesis and progression of kidney damage.

6. HCV and Chronic Kidney Disease: Evidence from the General Population

Renal involvement of hepatitis C virus infection was first reported two decades ago; however, knowledge of the association between HCV and low eGFR in the adult general population is limited and controversial. The prevalence of HCV among patients with CKD stage 5 (including patients on maintenance dialysis) is much higher than for the general population, and it is unknown whether this reflects an increased risk of viral exposure, a greater incidence and progression of kidney disease in individuals with HCV, or both.

The association between HCV infection with the prevalence and severity of chronic kidney disease in the adult general population has been addressed in several surveys derived from large databases (Table 2) [47–49]. Various cohort studies from developed countries have been published, some studies reported a positive association of HCV and CKD in the presence of cirrhosis in a population of veterans [12] or among national health insurance program users [50], but no such associations were identified in another population of veterans [9], an urban hospital population [10], and a private health insurance population [11]. Other cross-sectional surveys from the United States [51] and southern Taiwan [52] have yielded conflicting findings. We have performed a systematic review with a meta-analysis of observational studies (nine clinical studies; 817,917 unique individuals) to determine whether HCV is associated with increased likelihood of kidney disease in the general population [34]. We retrieved only studies performing multivariate analysis to provide the independent effect of anti-HCV serologic status on the incidence or prevalence of an estimated GFR (<60 mL/min per 1.73 m²) in the general population. Pooling of study results demonstrated the absence of a relationship between positive anti-HCV serologic status and reduced GFR (<60 mL/min/ 1.73 m²) in the general population (adjusted relative risk (aRR), 1.12; 95% CI, 0.91; 1.38; $P = 0.28$) according to the random-effects model [34]. We have now updated our systematic review of the published medical literature, and we retrieved longitudinal studies ($n = 7$; 890,560 unique individuals). A relationship between anti-HCV seropositivity and incidence of reduced eGFR (adjusted relative risk, 1.70; 95% CI, 1.20; 2.39; $P = 0.002$) in the adult general population was noted; substantial heterogeneity ($R_i = 0.98$; P -value by Q -test, <0.0001) was detected without publication bias (Figure 1). Thus, these findings support consistently an adverse effect of HCV on the development of chronic kidney disease in the general population. The most important shortcoming of these meta-analyses is that all the studies included had an observational design. Although much has been learned on the outcome of HCV in patients with chronic kidney disease or intact kidney function, the available data are of limited nature due to the lack of controlled studies that provide baseline data and sequential follow-up, in patients

TABLE 2: Impact of HCV on eGFR in the adult general population.

Author	Patient, <i>n</i>	aRR	Country	Reference year
Tsui et al. [9]	474,369	2.80 (2.43; 3.23)	Taiwan	2007
Moe et al. [10]	7,038	1.02 (0.90; 1.15)	US	2008
Asrani et al. [11]	88,822	0.92 (0.79; 1.08)	US	2010
Butt et al. [12]	43,139	1.3 (1.23; 1.37)	US	2011
Hofmann J. et al.	223,536	4.6 (3.7; 5.8)	Sweden	2011
Su F. et al.	37,746	1.53 (1.17; 2.01)	Taiwan	2012
Chen Y. et al.	15,910	1.75 (1.25; 2.43)	Taiwan	2013

eGFR: estimated glomerular filtration rate.

FIGURE 1: Funnel plot of precision by point (log).

with initially intact kidney function and HCV. These meta-analyses are potentially biased by additional issues. The cross-sectional design of many studies did not allow drawing conclusions on causality; also, the studies included in these meta-analyses might give incomplete information on additional unmeasured confounders that could introduce bias into the analysis. A magnitude of missing data or insensitive codes for comorbid diagnoses are inherent to clinical databases opposed to research databases. Additional limitations are that most surveys were from the United States and Taiwan and various populations (including veterans or inner city residents) have been evaluated. Finally, we cannot rule out an underestimation of negative results related to publication bias (positive relationships published more than negative ones).

7. HCV and Development of Chronic Kidney Disease: Additional Evidence

The detrimental role of HCV on the progression of chronic renal disease has been observed from sources other than the adult general population. Cohort studies performed in diabetic patients, individuals with HIV and HCV coinfection, and cirrhotics who completed IFN therapy demonstrated a relationship between positive anti-HCV serologic status and accelerated progression of chronic kidney disease. Soma et al. [53] evaluated 123 patients with biopsy-proven type II diabetic-related glomerulosclerosis (19.5%) over a follow-up

period of 27.6 ± 13.3 months; anti-HCV positive serologic status was an independent and significant risk factor of progression of chronic kidney disease by multivariable analysis (-0.1828 , 95% CI, -0.2787 ; -0.0869 ; $P < 0.0001$).

Mocroft et al. [54] found that the odds of progressive CKD were increased in participants with HCV (adjusted OR, 1.72; 95% CI, 1.07; 2.76) among 3,441 HIV positive, antiretroviral-treated clinical trial participants. Progressive CKD was defined as the composite of end-stage renal disease, renal death, or significant glomerular filtration rate (eGFR) decline (25% decline to eGFR <60 mL/min/1.73 m² or 25% decline with a baseline <60 mL/min/1.73 m²). In addition to conventional risk factors for chronic kidney disease such as aging, obesity, arterial hypertension, and diabetes mellitus, HCV infection may be an additional factor. This view is promoted by the notion that conventional risk factors only partially explain the excess risk of chronic kidney disease in the general population.

In the survey of Arase et al. [55], 650 patients with HCV-related cirrhosis were followed up for a mean period of 6.5 years after completing IFN therapy. Nonclearance of HCV was linked to the development of chronic kidney disease (eGFR of <60 mL/min per 1.73 m²), adjusted HR, 2.67 (95% CI, 1.34; 5.32, $P = 0.005$) [13].

8. HCV and Development of Chronic Kidney Disease: Potential Mechanisms

Various mechanisms have been cited to explain the adverse impact of anti-HCV seropositive status on the development of chronic kidney disease in the adult general population. An accelerated atheromasic disease at kidney level instigated by HCV has been mentioned, among others. The atherogenic activity of HCV has been also suggested to explain the adverse impact of HCV on the survival of patients undergoing maintenance dialysis. We have recently performed a meta-analysis of observational studies (fourteen observational studies involving 145,608 unique patients on long-term dialysis); pooling of study results demonstrated that anti-HCV antibody was an independent and significant risk factor for death in patients on regular dialysis. The summary estimate for adjusted relative risk (all-cause mortality) was 1.35 with a 95% confidence interval (CI) from 1.25 to 1.47. Stratified analysis showed that the adjusted relative risk (aRR) for liver disease-related and cardiovascular mortality was 3.82 (95%

CI, 1.92; 7.61) and 1.26 (95% CI, 1.1; 1.45), respectively [56]. Only three reports gave detailed information on the relationship between anti-HCV serologic status and cardiovascular-related mortality, however, the size of the subgroup of studies was large ($n = 37,787$) with no significant heterogeneity. Thus, the excess risk of death in anti-HCV positive patients is related either to chronic liver disease (and its long-term complications such as cirrhosis and hepatocellular carcinoma) and cardiovascular mortality. Because patients on long-term dialysis have an exceptionally high short-term mortality, it is less likely that the HCV-associated death risk is only due to such long-term complications as liver disease. The excess risk of cardiovascular disease among anti-HCV positive patients undergoing maintenance dialysis has been attributed to an atherogenic role of HCV through the aggravation of individual components of the metabolic syndrome (hyperglycemia, insulin resistance, abdominal obesity, arterial hypertension, and dyslipidemia).

That HCV could prompt cardiovascular alterations in patients with chronic kidney disease (via direct and indirect mechanisms) has been suggested by the epidemiological evidence reported above and other additional data. Yelken et al. [57] measured coronary flow reserve (CFR) by transthoracic Doppler echocardiography in nondiabetic anti-HCV positive ($n = 26$) and negative ($n = 26$) patients undergoing regular dialysis (haemodialysis or peritoneal dialysis) after kidney transplant failure. Clinical and demographic characteristics were similar between the two groups. CFR was significantly lower in HCV-infected than uninfected individuals (1.5 ± 1.1 versus 1.63 ± 0.26 , $P = 0.03$).

Oyake and colleagues [58] evaluated 94 dialysis patients (17 being anti-HCV positive/HCV RNA positive) by prospective measurements of aortic stiffness using carotid-femoral pulse wave velocity (PWV). They found by multiple logistic regression analysis that mean blood pressure and HCV viremia (OR, 9.7; 95% CI, 1.18; 81.2, $P < 0.05$) were significantly and independently associated with high aortic PWV ($> \text{or} = 10.0$ m/sec, mean). During the follow-up period, 13 patients suffered from cardiovascular events. Kaplan-Meier survival curves for cerebrovascular and cardiovascular event-free rates indicated a highly significant difference between HCV-RNA positive or negative patients on dialysis (log-rank test, $P < 0.05$). The authors mentioned an atherogenic role of HCV through aggravation of metabolic syndrome and dyslipidemia.

9. HCV and Cardiovascular Diseases in the General Population: Novel Data

HCV infection is currently considered by some investigators as a systemic disease, for which clinicians must evaluate the anti-HCV positive patient either for liver disease and cardiovascular or cerebrovascular risk [59]. The strongest evidence of a relationship between chronic HCV infection and cardiovascular or cerebrovascular events in the adult general population has been generated by longitudinal studies evaluating the natural history of patients with chronic HCV. At least three prospective studies have found a significant

increase in cardiovascular mortality [60], frequency of stroke [61], and lethal cerebrovascular events [62], respectively, in anti-HCV positive compared to negative individuals with intact kidney function. In addition, at least four retrospective surveys have reported an excess in acute coronary artery syndrome [63], incidental coronary artery disease [64], stroke [65], and cardiovascular mortality [66] in anti-HCV positive compared to negative patients. Only one retrospective cohort study concluded that HCV was not an independent risk factor for acute myocardial infarction among adult followed in general practices in the United Kingdom [67].

The evidence coming from case control studies is more equivocal. Many authors found a relationship between HCV and carotid atherosclerosis [68–71], others a link between HCV and coronary atherosclerosis [72, 73] or myocardial dysfunction [74, 75]. However, some conflicting reports have been given [76–79]. Discrepancies between the observed results could likely be due to the characteristics of the studied populations and differences in the assessment of HCV infection (or its severity) or in the evaluation of carotid or coronary atherosclerosis. The potential confounding by unmeasured or inadequately controlled variables cannot be excluded.

Recent data from the medical literature suggest that HCV could prompt cardiovascular and peripheral vascular disease by multiple ways. Some metabolic alterations (i.e., obesity, insulin resistance, diabetes, steatosis, and dyslipidemia) have been reported more frequently in HCV infected compared with uninfected patients, due to the interferences played by HCV in the glucose and lipid metabolism [80–82]. Insulin resistance has been associated with endothelial dysfunction, abnormalities in nitric oxide production, and platelet dysfunction [83]; type 2 diabetes increases the cardiovascular risk via various mechanisms including increased platelet activity, foam cell formation, or glycation of the extracellular matrix, all of which can increase the risk for atherosclerosis [84]. In addition to these metabolic alterations, alternative mechanisms have been cited. It has been suggested that other infectious agents, via microinflammation, are involved in the pathogenesis of atherosclerotic lesions. As an example, Lin et al. performed a multistage sampling survey in Taiwan ($n = 3352$ participants, 687 with CKD); they found an independent and significant relationship between HBsAg seropositive status and reduced eGFR (adjusted OR, 1.35, 95% CI, 1.03; 1.77) and suggested that chronic infections *per se* may have an adverse impact on the progression of chronic kidney diseases [52]. Boddi et al. [85] detected positive strand HCV RNA in carotid plaques from anti-HCV positive patients but not in plaques of anti-HCV negative individuals and suggested an active local activity of HCV in the vascular tissue. In HCV chronically infected patients, the pathogenesis of liver damage is mostly immune mediated as the immune system is inadequate to eradicate the virus, and atherosclerotic lesions should be the result of the systemic activation of the immune system leading to chronic inflammation via both innate natural killer mediated and adaptive T helper 1 mediated responses [59].

10. Conclusions

Chronic renal disease is an important public health problem which significantly increases the likelihood of adverse outcomes and high health-care costs. HCV infection is both a cause and complication of chronic kidney disease, and recent data suggest a detrimental role of HCV in the development of chronic kidney disease in the adult general population. A number of studies reported a high frequency of metabolic comorbidities in anti-HCV positive patients which could at least partially explain the link between HCV seropositive status and a higher prevalence and severity of chronic kidney disease. The future availability of effective and safe therapies could lead to antiviral treatment of HCV infection both to cure liver damage and reduce extrahepatic complications of HCV, including the progression of CKD to late stages.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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